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EXAMINER	
PANDE, SUCHIRA	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,520	ANDERSEN ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8-18,22,23,43 and 44* is/are pending in the application.

4a) Of the above claim(s) *10-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-6, 8-9, 22-23, and 43-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Applicant has amended claim 1, cancelled claims 4, 7, 19-21, 24-42; and withdrawn claims 10-18. Consequently claims 1-3, 5-6, 8-9, 22-23, 43 and 44 are active and will be examined in this action.

Response to Arguments

Re 103 rejection of claims 1-3, 5-6, 8-9, 22-23 and 44 over Unger et al. ; Wang et al. ; Ohnishi et al.; Dolganov et al. and First et al.

2. Applicant's arguments filed August 29, 2008 have been fully considered but they are not persuasive. Applicant has amended base claim 1 to add limitation to the type of the labeled oligonucleotide probe used "---- and each of which is disposed between the ninety-five to one-thousand and thirteen primer sets amplifying a given target gene sequence of interest,". To the Examiner, it is not clear what kind of probe applicant is trying to claim by recitation of "---each of which is disposed between the--- ". In order to look for guidance in the specification, Examiner did a search for the terms "disposed" and "between". These searches did not indicate presence of any literal support in the specification for the newly added limitation. Hence Examiner is doing a new matter rejection to indicate the fact that the specification as filed lacks support for the newly added limitation. Since it is not clear to Examiner what the newly added limitation actually means, a 112 2nd rejection is being introduced to indicate the fact that as currently recited the base claim 1 does not indicate to one of ordinary skill the types of probes that are encompassed by current

invention. The newly introduced phrase ----each of which is disposed between the -----primer sets amplifying a given target gene sequence of interest, ---needs to be clarified in context of the instant claim.

Furthermore Applicant argues that the previously cited art is not applicable, in view of the newly added limitation described above. But Applicant provides no explanation as to why the cited art is not applicable. As explained above since Examiner can not figure out what the newly added limitation is referring to, hence to the Examiner it is not clear why the cited art is not applicable. Therefore, Examiner is maintaining the previously cited rejections.

Applicant also argues that the combination of references proposed by the Examiner would not provide a reasonable expectation of success. To support their assertion Applicant refers to sections of Rudi et al. nucleic acids research 2003 vol. 31, no 11 e62. This argument is not persuasive as teaching of Rudi et al. applies to the bipartite primers used by them in the MQDA-PCR method. The instant invention is not reciting use of bipartite primers nor is it reciting the MQDA-PCR method. Therefore the teachings of Rudi et al. can not be applied in the instant situation. Hence the cited art is still applicable.

Finally Applicant is arguing unexpected results without providing any data to support the allegations. Mere allegations of unexpected results are not convincing. Hence the previously cited 103 rejections of claims 1-3, 5-6, 8-9, 22-23 and 44 over Unger et al. ; Wang et al. ; Ohnishi et al.; Dolganov et al. and First et al. are being maintained.

Re 103 rejection of claims 43 over Unger et al. ; Wang et al. ; Ohnishi et al.; Dolganov et al. ; First et al. as applied to claim 1 above further in view of Heid et al.

3. Since rejection of claim 1 over Unger et al.; Wang et al.; Ohnishi et al.; Dolganov et al. and First et al. is being maintained. Therefore rejection of claim 43 further in view of Heid et al. is also being maintained.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 5-6, 8-9, 22-23, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding claim 1, Examiner could not find support for the newly added limitation "----and each of which is disposed between the ninety-five to one-thousand and thirteen primer sets amplifying a given target gene sequence of interest,"--- in the specification as filed. This is a NEW MATTER rejection.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 5-6, 8-9, 22-23, 43 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As currently recited the base claim 1 does not indicate to one of ordinary skill the types of probes that are encompassed by current invention. The newly introduced phrase ----each of which is disposed between the -----primer sets amplifying a given target gene sequence of interest, ---needs to be clarified in context of the instant claim. As recited currently the claim language does not indicate to one of ordinary skill what is meant by the phrase--- each of which is disposed between the -----primer sets ---". Thus rendering the meets and bounds of the type of oligo probe claimed unclear. Amendment to claim language to clarify the above issue is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-3, 5-6, 8-9, 22-23,and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. (US pat. 7,118, 910 B2 issued Oct, 10, 2006 with priority back to June 24, 2002) in view of Wang et al. (1998) Science 280: page 1077-1082; Ohnishi et al. (2001) J. Hum Genet 46:471-477; Dolganov et al. (2001) Genome Research 11:1473-1483 and First et al. (US Pat. 5,776,682 issued July 7, 1998).

Regarding claim 1, Unger et al. teach:

a method for quantifying the expression of target gene sequences of interest in a sample (see col. 22 line 41 where Quantitative RT-PCR is taught), comprising the steps of:

(i) amplifying ninety-five to one-thousand and thirteen (See col. 30 lines 17-21 where the array based device is taught for multiplexing large number of amplification reaction at the same time. By teaching multiplexing a large number, Unger et al. teach ninety-five to one-thousand and thirteen cDNA molecules derived from a sample by polymerase chain reaction in the presence of ninety-five to one-thousand and thirteen amplification primer sets suitable for amplifying target gene sequence of interest (see col. 28 lines 49-50 where cDNA reverse transcribed from an mRNA is taught), and

in the presence of ninety-five to one-thousand and thirteen oligonucleotide probes complementary to a region of an amplified target gene sequence, said ninety-five to one-thousand and thirteen oligonucleotide probes labeled with a labeling system suitable for monitoring the amplification reaction as a function of time, each of which is complementary to a region of a different amplified target gene sequence of interest (see col. 30 lines 49-55 where multiple expression analysis at each reaction site within this array device is taught using quantitative methods such as TaqMan. By teaching the TaqMan method for performing multiple expression analysis at each site Unger et al. teach oligonucleotide probes complementary to a region of an amplified target gene sequence, said oligonucleotide probes labeled with a labeling system suitable for monitoring the amplification reaction as a function of time, each of which is complementary to a region of a different amplified target gene sequence of interest. This is because TaqMan method is a method used to perform real time PCR which requires oligonucleotide probes complementary to a region of an amplified target gene sequence. These probes for each region have to be labeled with a labeling system suitable for monitoring the amplification reaction as a function of time—then only the real time analysis can be conducted. Since multiplex reaction is being conducted then the probes have to be complementary to a region of a different amplified target gene sequence of interest so that all the target regions of interest can be followed in the real time manner. See col. 22 lines 54-63 where details of labeled probes used in TaqMan assay are provided along with statement that both probe and PCR primers are included in the reaction mixture.

Thus indicating the PCR is conducted in presence of both primers and probes for the regions to be amplified and detected using real time quantitative PCR. Both the upstream and downstream primers flanking the region of interest along with a probe complementary to target nucleic acid are taught (see col. 22 lines 59-63),

and each of which is disposed between the ninety-five to one-thousand and thirteen primer sets amplifying a given target gene sequence of interest, (As explained above in 112 2nd rejection, its not clear what this newly added limitation is referring to hence it has not been addressed further) and

(ii) quantifying at least one of the target gene sequences amplified in step (i). in a real-time PCR (see col. 22 lines 41-53 where details of quantitative real time PCR using TaqMan are provided) in which the product of step (i) is divided into a plurality of aliquots and said real-time PCR quantifying in step (ii) is performed on said aliquots (see col. 22 lines 41-46 where quantity of a target nucleic acid present in a sample is taught to be determined by measuring the amount of amplification product **formed after the amplification process itself**. By teaching quantification after amplification process itself and teaching multiplex amplification can be performed within single reaction site suing different pairs of primers for different targets (see col. 30 lines 25-28), Unger et al. teach the product of step (i) is divided into a plurality of aliquots and said real-time PCR quantifying in step (ii) is performed on said aliquots. This is because the amount of each target that was present in the starting mix has to be determined from amplified mixture. So the amplified mixture from step (i) necessarily has to be divided into a plurality of aliquots (corresponding to the number of targets to be

quantified) and said real-time PCR quantifying in step (ii) is performed on said aliquots so that each target that was to be quantified can be analyzed),

wherein the quantifying in step (ii) comprises PCR amplifying with at least one of the primer pairs in step (i) and at least one of the oligonucleotide probes in step (i). (Since Unger et al. teaches real time PCR as explained above that method requires that the PCR amplification takes place with the pair of primers that will amplify the target to be quantified and the probe that is specific for that given target be also present).

Regarding claim 6, Unger et al teach thermostable DNA polymerase. (See col. 25 lines 6-17)

Regarding claim 8, Unger et al teach wherein label is a fluorophore (see col. 34 lines 53-67 where FAM and VIC are taught as fluorophore label).

Regarding claim 9, Unger et al teach in which said at least one oligonucleotide probe is selected from the group consisting of 5'-exonuclease probes, stem-loop beacon probes (see col. 33 line 61 where TaqMan probe is taught—this is a 5'-exonuclease probe and see col. 23 line 37-60 where molecular beacon probes are taught).

Regarding claim 1 Unger et al. teach multiplex PCR with many targets but do not explicitly recite the number "ninety-five to one-thousand and thirteen" in context of the numbers of cDNA recites in the claim; they also do not recite this number in context of the labeled oligonucleotide probes; similarly they do not recite this number in context of the number of primer pairs used to amplify the targets .

With regards to claim1, Unger et al. does not teach following:

express recitation of ninety-five to one-thousand and thirteen targets;

the primers flanking the above numbered targets which corresponds to ninety-five to one-thousand and thirteen primer pairs; and

ninety-five to one-thousand and thirteen labeled oligos that will be suitable probes for each of the above targets to be quantified by real time PCR method;

wherein each primer of the ninety-five to one-thousand and thirteen PCR primer pairs in step (i) is present at a concentration of 30-45 picomolar.

Regarding claim 1, Wang et al. teach detection of 2748 candidate SNPs after amplification of sample from an individual—meaning amplification of at least 2748 targets are taught from one individual sample. Each target amplification requires two primers (upstream and downstream therefore teaching 2748 pairs of primers. Therefore art teaches amplification and detection of at least 2748 targets using 2748 pairs of primers corresponding to the targets in the sample. (see whole article specially page 1078 last col. Par. 2 and 3).

Regarding claim 1, by teaching detection of 2748 targets from a sample, Wang et al. teach amplification of ninety-five to one-thousand and thirteen targets; the primers flanking the above numbered targets which corresponds to ninety-five to one-thousand and thirteen primer pairs. Since ninety-five to one-thousand and thirteen targets are taught. To quantify these many targets corresponding number of oligonucleotide probes will be necessarily required during real time PCR. Wang et al. also teaches multiplexing (see page 1082 footnote 26 where multiplex PCR is taught.)

Regarding claims 22 & 23, Wang et al. teach a multiplexing PCR method wherein an observed efficiency of amplification is 96 % (see page 1080 par. 4 where 96% of the 512 loci assayed using multiplex PCR amplification were correctly read in 100% of individuals). Thus teaching wherein an observed efficiency of amplification is greater than 70% (claim 22) and the observed efficiency of amplification is greater than 90% (claim 23).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Wang et al. in the method of Unger et al. at the time the invention was made. The motivation to do so is provided to one of ordinary skill by art itself (as exemplified by Ohnishi et al.) and by Dolganov et al.

Art teaches 100ng of genomic DNA is required to assay a single SNP. Therefore, only 1000SNPs can be genotyped from 100 μg of genomic DNA (equivalent to a 5- to 10 ml sample of whole blood). Hence this assay is not applicable for SNP genotyping on the very large scale needed for genome-wide association studies, for which 50,000-300,000 SNPs should be typed in each individual's DNA. To reduce the amount of DNA required to less than 1 ng for the assay of a single SNP and to make genome-wide association studies feasible, we combined a multiplex PCR method with the invader assay" (see Ohnishi et al. (2001) J. Hum Genet. 46;471-477 page 471 par. 2-3 introduction). They go on to state "We amplified 100 genomic DNA fragments, each containing one SNP, in a single tube" (see abstract). Thus art teaches multiplexing of 100 targets in one tube.

Wang et al. teaches amplification of 2748 targets from single sample. Wang et al teaches use of multiple arrays on chips to detect these many targets.

Regarding claim 1, Dolganov et al. teaches a method for quantifying the expression of target gene sequences of interest in a sample (see page 1473, par. 2 where real time PCR quantification is taught), comprising the steps of:

(i) amplifying cDNA (see page 1473, par. 1 where a two step process incorporating multiplex PCR (typically with a mix of 100 –300 gene specific primer sets) followed by real time PCR on generated cDNA product is taught, thus by teaching 300 cDNA amplification Dolganov et al. teach amplifying ninety-five to one-thousand and thirteen cDNA (as 300 cDNAs and corresponding nested primer sets and probes taught by Dolganov et al. falls within the range recited in the instant claims) molecules derived from a sample by polymerase chain reaction in the presence of a plurality of amplification primer sets suitable for amplifying target gene sequence of interest, and in the presence of ninety-five to one-thousand and thirteen oligonucleotide probes complementary to a region of an amplified target gene sequence, said ninety-five to one-thousand and thirteen oligonucleotide probes labeled with a labeling system suitable for monitoring the amplification reaction as a function of time each of which is complementary to a region of a different amplified target qene sequence of interest (See par. 2 where real time amplification PCR using 200 gene-specific primers is taught this inherently involves use of a labled probe labeled with a labeling system suitable for monitoring the amplification reaction as a function of time) (Also see page 1474, par. 1 and Fig. 1 where RT-PCR for 34 genes was

performed. Taqman hybridization probe is taught here which inherently indicates that it is complementary to a region of a different amplified target gene sequence. Taqman probe has fluorescein reporter dye at 5' end (FAM)). This along with the teaching above that Taqman primers and probes are used inherently teaches that probe used is complementary to a region of a different amplified target qene sequence of interest, and

(ii) quantifying the target gene sequences amplified in step (Gene quantification via real time PCR using nested Taqman primers is taught see legend of fig. 1) .

(i) wherein the amplifyinq of step (i) comprises ninety-five to one-thousand and thirteen PCR primer pairs (see above),

(ii) quantifying the target gene sequences amplified in step (i) (Gene quantification via real time PCR using nested Taqman primers is taught see legend of fig. 1) said quantifying comprises analysis by real-time polymerase chain reaction amplification (see page 1473 abstract where gene quantification via real-time PCR-based method is taught)

Dolganov et al. teaches a method in which the amplifying in step (i) is further carried out in the presence of an oligonucleotide probe complementary to a region of an amplified target gene sequence of interest, said probe being labeled with a labeling system suitable for monitoring the amplification reaction in step (i) as a function of time (see page 1474, par. 1 and Fig. 1 where RT-PCR for 34 genes was performed. Taqman hybridization probe is taught here which inherently indicates that it is complementary to a region of an amplified target

gene sequence. Taqman probe has fluorescein reporter dye at 5' end (FAM) which is suitable for real time detection see legend of fig. 1).

Dolganov et al. teaches a method in which the product of step (i) is divided into a plurality of aliquots and said quantifying in step (ii) is performed on said aliquots (see page 1474 par. 2).

Dolganov et al. teaches a method in which step (ii) comprises amplifying the product in one or more separate aliquots by polymerase chain reaction in the presence of an amplification primer set suitable for amplifying one of the target sequences of the plurality (see page 1474 par. 2 and fig. 1 where multiplex RT-PCR is followed by real time PCR).

Regarding claim 2, Dolganov et al. teaches generating RT-PCR for 34 genes as described above for claim 1 therefore it inherently teaches a method in which the amplification of step (i) is further carried out in the presence of a reverse transcriptase such that the polymerase chain reaction is reverse-transcription polymerase chain reaction and wherein the one or more cDNA molecules is obtained from mRNA derived from the sample.

Regarding claim 3, Dolganov et al. teaches a method in which the one or more cDNA molecules comprise a cDNA library (see page 1474 where 34 genes of varying abundance in the sample were reverse transcribed and the RT-PCR products were cloned into pCRII-TOPO vector is taught. Thus Dolganov et al. teaches a cDNA library).

Regarding claim 5, Dolganov et al. teaches the method wherein the polymerase chain reaction of step (i) is carried out for a number of cycles such

that amplification remains in the linear range (see page 1474 section validation of two step ---multiplex RT-PCR protocol and Fig. 2 on page 1475 where linearity of two step PCR protocol is taught. also See legend of fig. 1 on page 1474 where its taught that multiplex PCR is monitored carefully to evade plateau phase of PCR).

Regarding claim 6, Dolganov et al. teaches where the amplification in step (i) is achieved with a thermostable DNA polymerase (see page 1481 where Klen-Taq DNA polymerase is taught as a thermostable DNA polymerase).

Regarding claim 44, Dolganov et al. teach amplifying the cDNA molecules comprises as many as fourteen cycles (see fig. 6 where 10 to 25 cycles are shown. The data in graph includes amplifying the cDNA molecules comprises as many as 14 cycles).

Dolganov et al. state" we have developed a novel two-step RT-PCR approach for transcriptional profiling of multiple low –abundance mRNAs that requires significantly less starting RNA than conventional TaqMan approaches. This improved sensitivity allows transcriptional profiling in small biologic samples, such as 1-100 cells. The method relies on final gene quantification via-real time PCR using cDNA product generated by controlled hot start multiple RT-PCR approach. In contrast with conventional TaqMan approach, this method requires lower amounts of starting RNA and therefore could be applied to quantify multiple low expressed genes in small clinical samples" (see page 1477 last par.). They go on to state "the proposed method has two important advantages over conventional quantitative PCR, TaqMan assays, and gene microarrays. First, the new method allows simultaneous quantification of hundreds of transcripts using

as little as 2.5 fg of total RNA per gene whereas conventional TaqMan assays require substantially larger amounts of total RNA, usually from 10 ng to 1 mg per reaction, depending on the abundance of the genes of interest.-----Second, in contrast with gene microarray methods that have a much smaller dynamic range, lower specificity and sensitivity, real –time PCR has a dynamic range of more than six orders of magnitude and allows simultaneous accurate measurements of low- and high-abundance mRNAs." (see Dolganov et al. page 1479 last par.).

Since the number of targets claimed in the instant invention fall in the range taught by prior art as something that is feasible to amplify in multiplex reactions (Ohnishi et al. teaches amplification of 100 targets and Wang et al teaches amplification of 2748 targets). Thus by combining the method of Wang et al. in the method of Unger et al. one has a reasonable expectation of success that ninety-five to one-thousand and thirteen cDNA targets can be amplified in the microfluidic apparatus taught by Unger and quantified using the real-time method taught by Unger.

Regarding claim1 neither Unger et al. nor Wang et al. or Dolganov et al. teach wherein each primer of the PCR primer pairs in step (i) is present at a concentration of 30-45 picomolar.

Regarding claim 1, First et al. teach use of primer pairs in the concentration of 30-45 picomolar in multiplex PCR reactions (see Table 2 where preferred primer concentrations are taught. See primer pairs identified by SEQ ID 5 and 6 where 35 pM conc is taught; SEQ ID 21 and SEQ ID 22, SEQ ID 23 and 24 are used at 36.5 pM each; SEQ ID 97 and 98 are used at 44.5 pM each).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of First et al. in the method of Unger et al., Wang et al, Ohnishi et al and Dolganov et al. at the time the invention was made. The motivation to do so is provided to one of ordinary skill both by Dolganov et al. and First et al.

In the section relating to Real-Time PCR Dolganov et al. state "Typically, an equivalent of 2.5 fg to 10 pg of total RNA was used in 25 μl of universal Master Mix. All forward and reverse TaqMan primers were optimized" (see page 1481 last par.). Thus Dolganov et al. teach to one of ordinary skill that optimization is performed for all primers. They do not specifically state the parameters that are optimized and the range of values associated with them.

First et al. provide specific guidance to one of ordinary skill in the art by stating "it must be noted that these primer concentrations are the preferred concentrations. Variations maybe made in the concentration of the various primer concentrations to optimize PCR" (see col. 18, lines 25-27). Thus providing explicit guidance to one of ordinary skill that the range of concentrations taught by First et al. work well for the various primers used by them and the practitioner with an ordinary skill in the art may adjust the primer concentration down to as low 30-45 pM each in multiplex PCR reactions."

11. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al.; Wang et al.; Ohnishi et al.; Dolganov et al. and First et al. as applied to claim 1 above, and further in view of Heid et al. (1996) Genome Research 6: 986-994.

Regarding claim 43, Unger et al.; Wang et al.; Ohnishi et al.; Dolganov et al. and First et al. teach the method of claim 1, but do not teach the method in which amplification is carried out in the presence of uracil-N-glycosylase.

Regarding claim 43, Heid et al. teaches method of claim 1 in which the amplification is carried out in the presence of uracil N-glycosylase (see page 993 par. 3 where AmpErase uracil N-glycosylase is taught).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Heid et al. in the method of Unger et al.; Wang et al.; Ohnishi et al.; Dolganov et al. and First et al. at the time the invention was made. The motivation to do so is provided to one of ordinary skill by Heid et al.

Heid et al state " we have developed a novel 'real –time" quantitative PCR method.---Unlike other quantitative PCR methods, real –time PCR does not require post-PCR sample handling, preventing potential PCR product carry over contamination and resulting in much faster and higher throughput assays" (see abstract).

Conclusion

12. All claims under consideration 1-3, 5-6, 8-9, 22-23 and 43- 44 are rejected over prior art.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

Suchira Pande
Examiner
Art Unit 1637